STN- Structure Search
4-19-05

10/658,298

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L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:220202 CAPLUS
DOCUMENT NUMBER: 140:253561
TITLE: Preparation of 1,2-dihydropyrazol-3-ones and 3-alkoxy-1H-pyrazoles as TNF-α and interleukin lowering agents for the treatment of inflammation
INVENTOR(S): Dominguez, Celia; Zhang, Dawei; Sham, Kelvin K. C.; Cao, Guo-qiang
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022055	A1	20040318	WO 2003-US28067	20030908
WO 2004022055	B1	20050113		
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004058918	A1	20040325	US 2003-658298	20030908

PRIORITY APPLN. INFO.: US 2002-409176P P 20020909
OTHER SOURCE(S): MARPAT 140:253561
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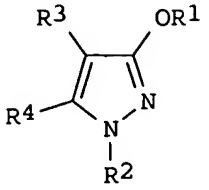

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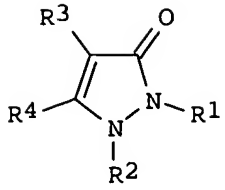

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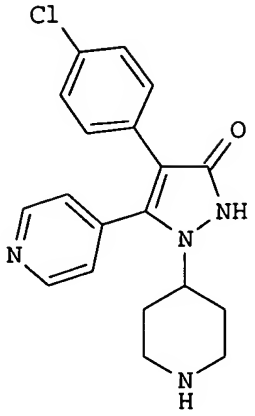

III

AB The invention discloses the preparation of title compds. I and II [wherein R1 = H or alkyl; R2 = alkyl, Ph, PhCH2, (alkyl)Rc, (alkyl)Rf, or Rg; R3 and R4 = independently (un)substituted Ph, naphthyl, or heterocyclyl; Rc = independently (un)substituted heterocyclyl; Rf = substituted Rc; Rg = substituted alkyl, Ph, or PhCH2; and pharmaceutically acceptable salts thereof] as tumor necrosis factor α (TNFα) and interleukin 1, 6, and 8 (IL-1, IL-6, and IL-8) inhibitors. For example, (4-chlorophenyl)acetic acid was condensed with pyridine-4-carbaldehyde in acetic anhydride and TEA to give 2-(4-chlorophenyl)-3-(pyridin-4-yl)acrylic acid, which was esterified with MeOH in thionyl chloride. Cyclization of the acrylate with hydrazine in EtOH, followed by Pd/C catalyzed reduction, afforded 4-(4-chlorophenyl)-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one. Addition of 4-oxopiperidine-1-carboxylic acid tert-Bu ester in chloroform using sodium triacetoxy boron hydride, hydrogenation using Pd/C in EtOH, and deprotection with HCl in ether and dioxane gave III.. Selected compds. of the invention inhibited lipopolysaccharide-activated TNF production in THP1 cells with IC50 values of <20 μM. Also disclosed is a method of prophylaxis or treatment of inflammation, rheumatoid arthritis, Paget's disease, osteoporosis, multiple myeloma, uveitis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses, or herpes zoster infection in a mammal comprising administering an effective amount of I or II or their pharmaceutical compns. (no data).

IT **671780-98-6P**, 4-(4-Chlorophenyl)-1-[(piperidin-4-yl)methyl]-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one **671780-99-7P**,

4-(4-Chlorophenyl)-1-methyl-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one **671781-11-6P**, 4-(3,4-Dichlorophenyl)-1-isopropyl-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one **671781-24-1P**, 4-(Naphthalen-2-yl)-1-(3-phenylpropyl)-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one **671781-25-2P**, 4-(Naphthalen-2-yl)-1-(3-phenylpropyl)-5-pyridin-1,2-dihydropyrazol-3-one
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(TNFα and/or IL inhibitor; preparation of dihydropyrazolones and alkoxypyrazoles as TNF-α and interleukin lowering agents for treatment of inflammation and related conditions)

RN 671780-98-6 CAPLUS
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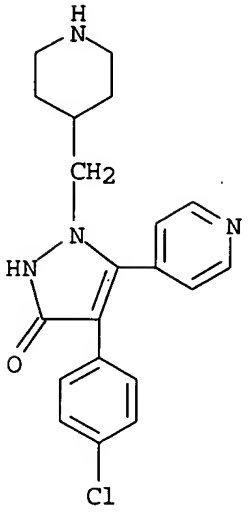

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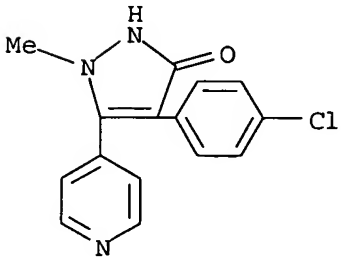

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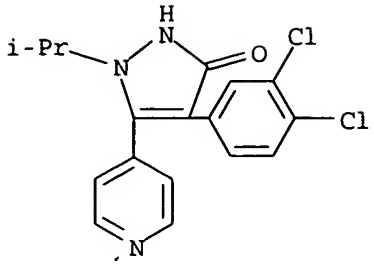

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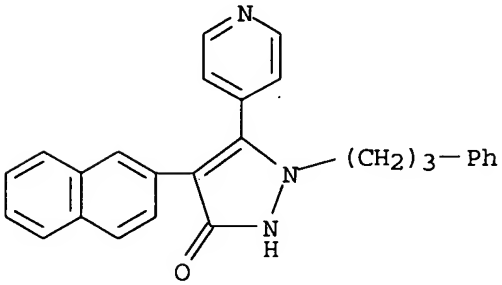

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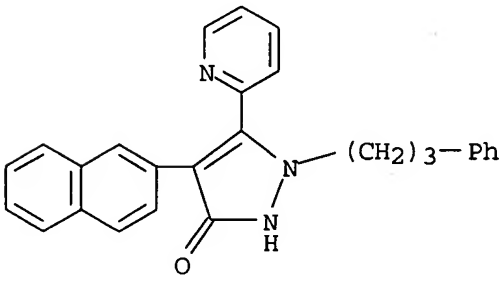

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
RE
(1) Abbott Lab; WO 9951580 A 1999 CAPLUS
(2) Abbott Lab; WO 0116138 A 2001 CAPLUS
(3) Asahi Kasei Kogyo Kabushiki Kaisha; US 4268626 A 1981 CAPLUS
(4) Aurich, H; CHEMISCHE BERICHTE 1965, V98(12), P3917 CAPLUS
(5) Boberg, F; JUSTUS LIEBIGS ANNALEN DER CHEMIE 1970, V734, P173 CAPLUS
(6) Bristol-Myers Squibb Co; WO 0059506 A 2000 CAPLUS
(7) Capuano, L; CHEMISCHE BERICHTE 1978, V111(7), P2497 CAPLUS
(8) Downs, J; JOURNAL OF HETEROCYCLIC CHEMISTRY 2001, V38(3), P695 CAPLUS

(9) Dymek, W; ACTA POLONIAE PHARMACEUTICA 1966, V23(4), P339 CAPLUS
(10) Dymek, W; ACTA POLONIAE PHARMACEUTICA 1967, V24(2), P97 CAPLUS
(11) Procter & Gamble; WO 03024970 A 2003 CAPLUS
(12) Procter & Gamble; WO 03080184 A 2003 CAPLUS
(13) Sandstrom, J; ARKIV FOER KEMI 1960, V15, P195 CAPLUS
(14) Searle & Co; WO 9852937 A 1998 CAPLUS
(15) Searle & Co; WO 9852941 A 1998 CAPLUS
(16) Smithkline Beecham; WO 9856377 A 1998 CAPLUS
(17) Sterling Drug Inc; EP 0299407 A 1989 CAPLUS
(18) Sterling Drug Inc; EP 0388690 A 1990 CAPLUS
(19) Toda, T; HETEROCYCLES 1987, V25(1), P79 CAPLUS

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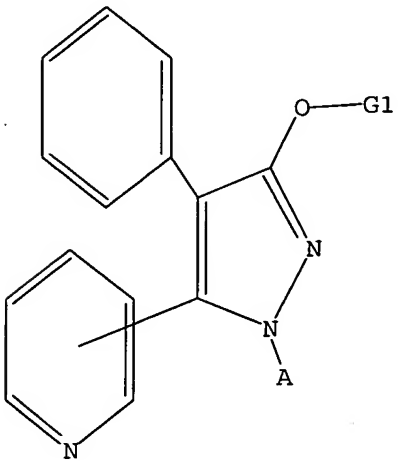


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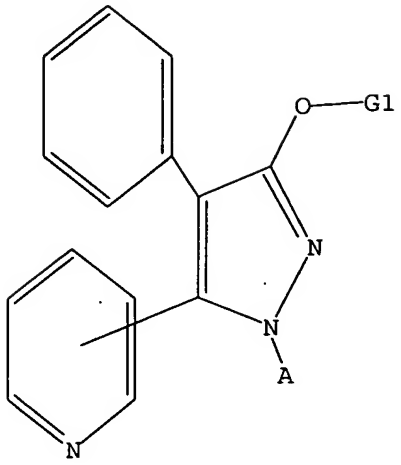

G1 H,Ak

Structure attributes must be viewed using STN Express query preparation.

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DOCUMENT NUMBER: 140:253561
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PATENT ASSIGNEE(S): Amgen Inc., USA
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FAMILY ACC. NUM. COUNT: 1
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WO 2004022055	B1	20050113		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
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US 2004058918	A1	20040325	US 2003-658298	20030908
PRIORITY APPLN. INFO.:			US 2002-409176P P	20020909
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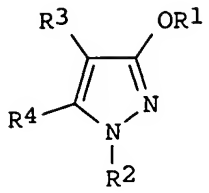

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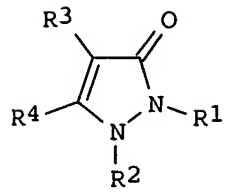

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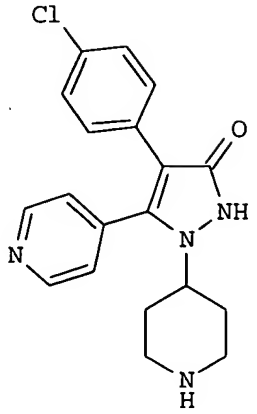
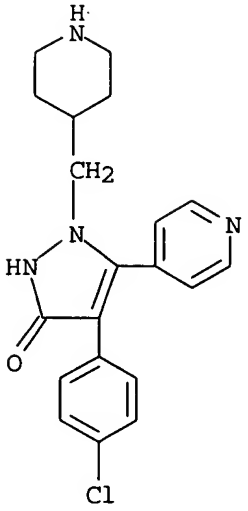


III

AB The invention discloses the preparation of title compds. I and II [wherein R1 = H or alkyl; R2 = alkyl, Ph, PhCH2, (alkyl)Rc, (alkyl)Rf, or Rg; R3 and R4 = independently (un)substituted Ph, naphthyl, or heterocyclyl; Rc = independently (un)substituted heterocyclyl; Rf = substituted Rc; Rg = substituted alkyl, Ph, or PhCH2; and pharmaceutically acceptable salts thereof] as tumor necrosis factor α (TNFα) and interleukin 1, 6, and 8 (IL-1, IL-6, and IL-8) inhibitors. For example, (4-chlorophenyl)acetic acid was condensed with pyridine-4-carbaldehyde in acetic anhydride and TEA to give 2-(4-chlorophenyl)-3-(pyridin-4-yl)acrylic acid, which was esterified with MeOH in thionyl chloride. Cyclization of the acrylate with hydrazine in EtOH, followed by Pd/C catalyzed reduction, afforded 4-(4-chlorophenyl)-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one. Addition of 4-oxopiperidine-1-carboxylic acid tert-Bu ester in chloroform using sodium triacetoxy boron hydride, hydrogenation using Pd/C in EtOH, and deprotection with HCl in ether and dioxane gave III. Selected compds. of the invention inhibited lipopolysaccharide-activated TNF production in THP1 cells with IC50 values of <20 μM. Also disclosed is a method of prophylaxis or treatment of inflammation, rheumatoid arthritis, Paget's disease, osteoporosis, multiple myeloma, uveitis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses, or herpes zoster infection in a mammal comprising administering an effective amount of I or II or their pharmaceutical compns. (no data).

IT **671780-98-6P**, 4-(4-Chlorophenyl)-1-[(piperidin-4-yl)methyl]-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one **671780-99-7P**, 4-(4-Chlorophenyl)-1-methyl-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one **671781-11-6P**, 4-(3,4-Dichlorophenyl)-1-isopropyl-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one **671781-13-8P**, 4-(3,4-Dichlorophenyl)-1-isopropyl-2-methyl-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one **671781-15-0P**, 4-(3,4-Dichlorophenyl)-2-methyl-5-(pyridin-4-yl)-1-[(pyridin-3-yl)methyl]-1,2-dihydropyrazol-3-one **671781-18-3P**, 1-Cyclohexylmethyl-4-(3,4-dichlorophenyl)-2-methyl-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one **671781-24-1P**, 4-(Naphthalen-2-yl)-1-(3-phenylpropyl)-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one **671781-25-2P**, 4-(Naphthalen-2-yl)-1-(3-phenylpropyl)-5-pyridin-1,2-dihydropyrazol-3-one
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(TNFα and/or IL inhibitor; preparation of dihydropyrazolones and alkoxypyrazoles as TNF-α and interleukin lowering agents for treatment of inflammation and related conditions)

RN 671780-98-6 CAPLUS
CN 3H-Pyrazol-3-one, 4-(4-chlorophenyl)-1,2-dihydro-1-(4-piperidinylmethyl)-5-(4-pyridinyl)- (9CI) (CA INDEX NAME)



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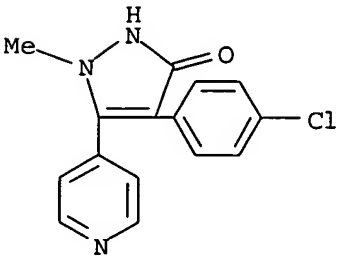

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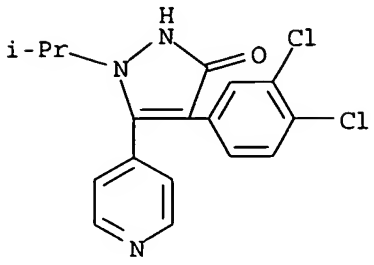

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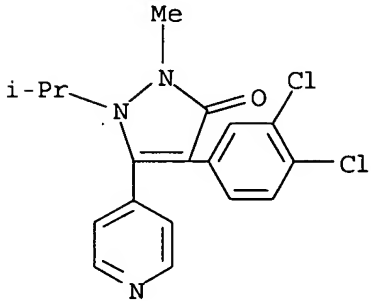

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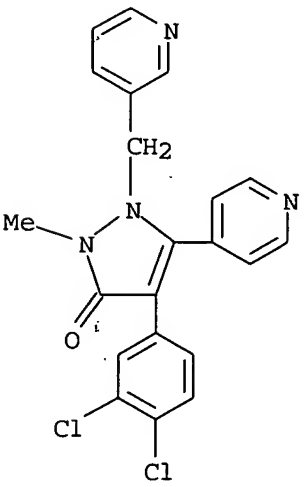

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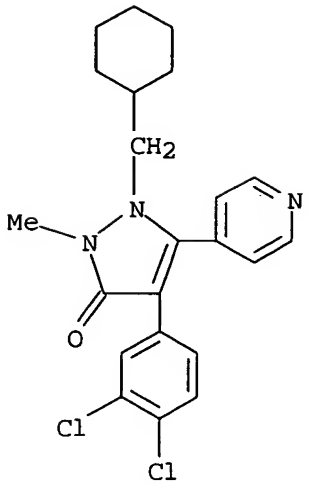

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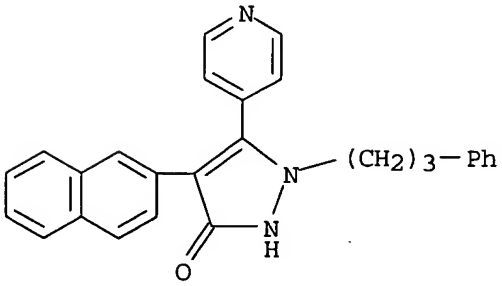

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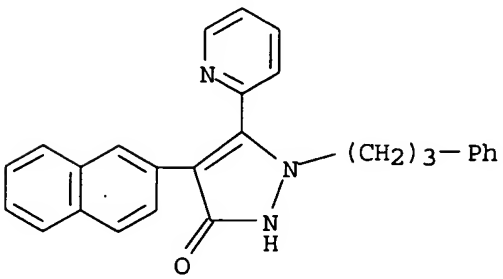

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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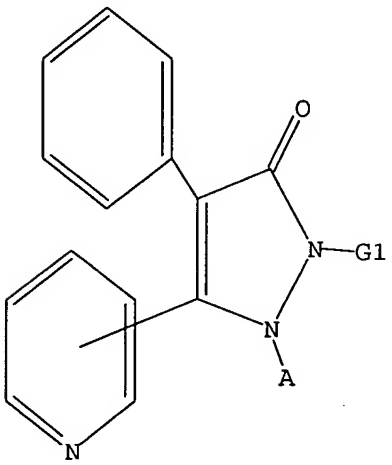

G1 H,Ak

Structure attributes must be viewed using STN Express query preparation.

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